GENERATORS OF PATHOLOGICALLY ENHANCED EXCITATION AS DETERMINANT STRUCTURES IN THE SPINAL CORD

G. N. Kryzhanovskii,* V. N. Grafova, and E. I. Danilova

With the aid of tetanus toxin, which disturbs various types of inhibition, generators of excitation were created in the left and right anterior horns of the lumbar spinal cord in rats. The regimes of activity of the generators differed: the left-sided generator, formed during the longer action of the toxin, in response to activation by trigger stimulation first produced tonic, and then intermittent activity, or individual spontaneous discharges, whereas the right-sided generator produced only tonic activity. If one generator was blocked by glycine, the other continued to operate as before. Activation of one generator led to concomitant depression of the effects of the other. During separate activation of each generator, all the spinal and supraspinal motoneuron pools synchronously reproduced the character of activity of the generator functioning at that particular moment. The generator thus played the role of a determinant structure, determining the behavior of the system. The results are examined from the standpoint of the general concept of the role of determinant structures in the activity of the nervous system and the theory of generator mechanisms of neuropathological syndromes characterized by hyperactivity of systems.

KEY WORDS: determinant; generator of enhanced excitation; spinal cord; tetanus toxin; glycine; strychnine-like tetanus.

Structures of the CNS forming an enhanced functional volley determine the character of activity of other parts of the CNS receiving that volley and thereby determine the behavior of the whole functional system which they activate [4, 6, 9-13]. These structures have been called determinant dispatch stations (DDS) or determinants. They were first found during analysis of spinal cord activity under conditions when inhibition was disturbed in the interneuron population, which acquired the properties of a DDS [1, 3, 7, 13, 16], working as generators of enhanced excitation [5, 11, 13-15]. Since this phenomenon reflects one of the principles of activity of the nervous system [4, 9-12], it was important to analyze it in more detail.

EXPERIMENTAL METHOD

Experiments were carried out on 36 noninbred albino rats weighing 200-220 g. Inhibition in the spinal cord was disturbed by injecting tetanus toxin into the leg muscles, from which the toxin traveled along the sciatic nerve to the anterior horns of the lumbar segments of the spinal cord [2, 8]. Local disturbance of inhibitory mechanisms in the population of motoneurons [2, 3, 8, 17, 18, 21-23] and of propriospinal neurons [2, 3, 16] arises in these zones and, under these circumstances, the interneuron population is converted into a hyperactive structure [4, 6, 7, 13, 16], the character of whose activity depends on the duration of action of the toxin. This feature was used as the functional marker of two hyperactive structures which were created in the two halves of the lumbar segments: Toxin (40 MLD for mice) was injected into the left gastrocnemius muscle 96 h, and into the right muscle 48 h, before investigation of the electrical activity of the muscles. Simultaneously

*Corresponding Member, Academy of Medical Sciences of the USSR.

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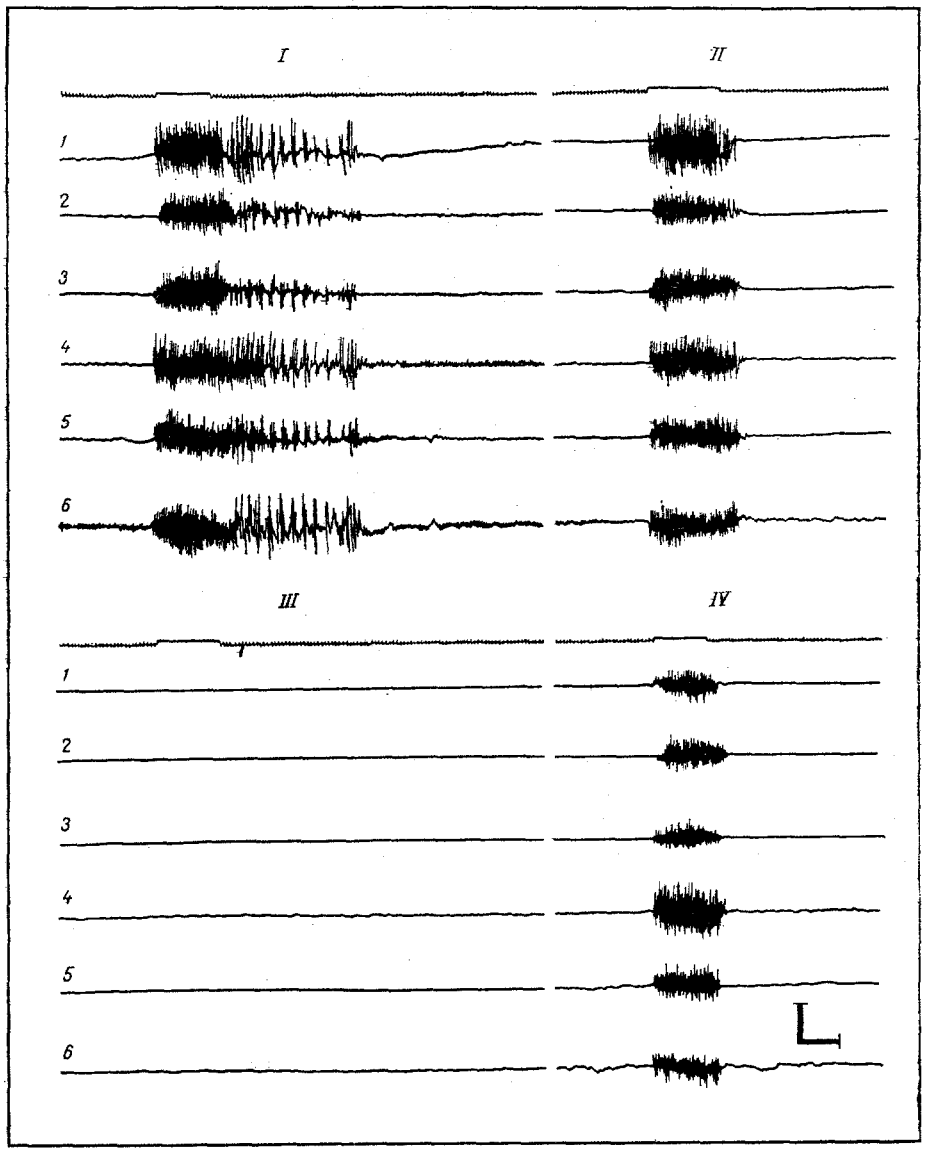

Fig. 1. Electrical activity in various muscles in response to nociceptive stimulation (squeezing toes with forceps) of left (I, III) and right (II, IV) hind limbs before (I, II) and after (III, IV) injection of glycine into left anterior horns L4-L6. 1, 2) Right and left neck muscles; 3, 4) right and left spinal muscles; 5, 6) posterior group of muscles of right and left thigh. Time of application of stimulus indicated by upward movement of top line. Calibration: stimulus 500 μV, time 1 sec.

with the toxins, antitoxin (0.025 IU) was injected intravenously to prevent the toxin from spreading via the blood stream [2, 7]. The electrical activity of the muscles was recorded on an eight-channel electroencephalograph (San'ei Instrument) through bipolar needle electrodes. For trigger activation of the generators, nociceptive stimulation was used (squeezing the digits or a fold of skin on the back). The generators were inhibited by glycine, which produces effects of postsynaptic inhibition [22-25]. Glycine was injected into the region of the generator (the anterior horns of segments L4-L6) by three punctures with a micromanipulator (10^{-4} ml of a 20% solution, pH 6.0, at each injection). In control experiments physiological saline or other amino acids in corresponding concentrations and with the same pH value were injected.

EXPERIMENTAL RESULTS AND DISCUSSION

After nociceptive stimulation of the left and right limbs, a burst of electrical activity was recorded in the muscles of the trunk, limbs, and neck (Fig. 1). This activity arose in virtually all the muscles on both sides, evidence of activation of motoneurons at all levels of the spinal cord. It could also be recorded in the muscles

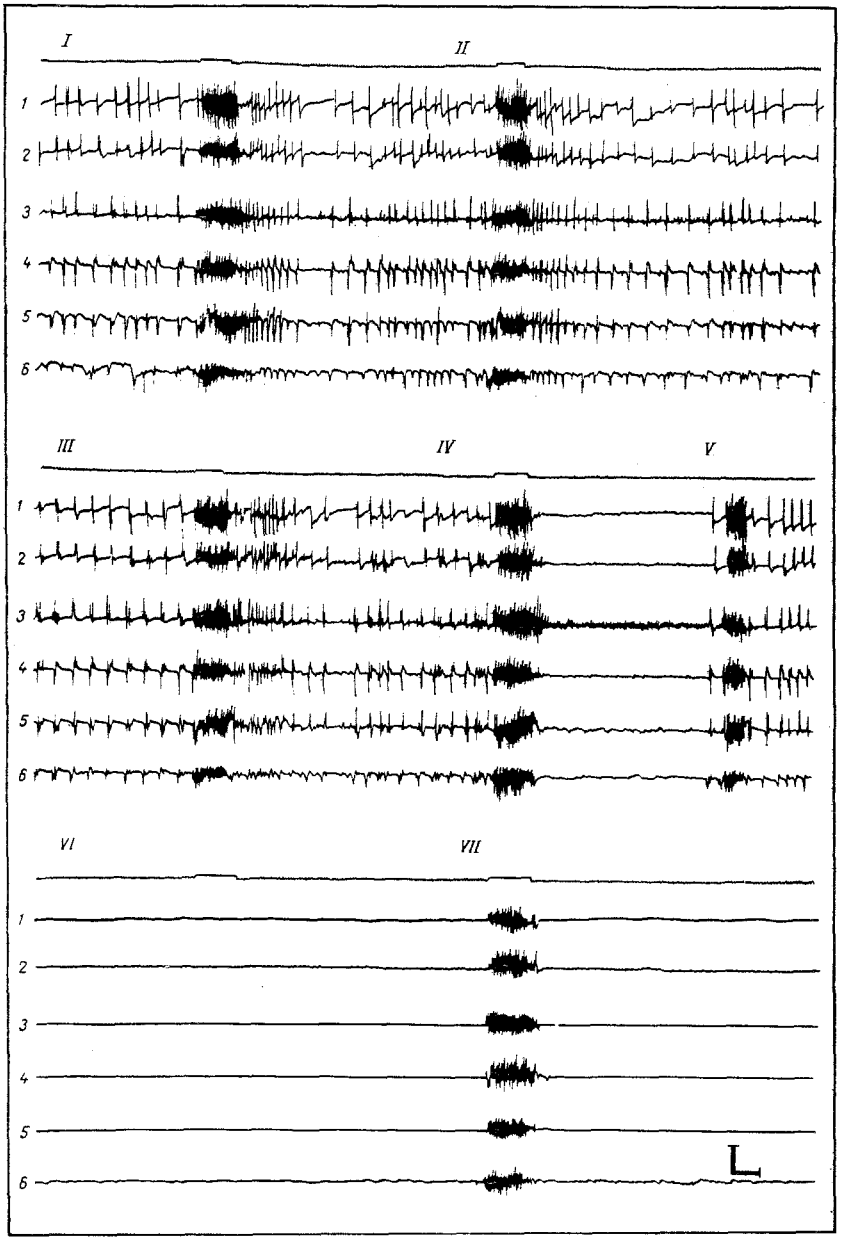

Fig. 2. Spontaneous discharges and tonic activity in various muscles in response to activation of left-sided and right-sided excitation generators. I, III) Synchronized discharges arising spontaneously and after activation of left-sided generator, and evoked tonic activity to activation of same generator; IV) evoked tonic activity to activation of right-sided generator and inhibition of spontaneous synchronized discharges generated by left-sided generator; V) spontaneous burst of tonic activity and spontaneous discharges; VI) inhibition of activity of left-sided generator by glycine: disappearance of spontaneous discharges and of evoked tonic activity; VII) evoked tonic activity during activation of right-sided generator. Remainder of legend as in Fig. 1.

of the head and in the muscles of mastication, indicating excitation of motoneurons in the brain stem. The evoked activity had the following distinguishing features: It appeared and disappeared virtually simultaneously in all muscles; its character was the same in all muscles in the case of both tonic activity and of separate discharges, which were synchronized in all the muscles; it continued for a long period of time after the end of stimulation.

These distinguishing features point to a single source of the evoked activity in the muscles. This source produces excitation of a definite pattern, imposes the character of its activity on all spinal and supraspinal motoneurons, and thus plays the role of a DDS or determinant.

The fact that electrical activity with a high amplitude and a high frequency was recorded in the muscles is evidence of involvement of many motoneurons in each nucleus in the response. This means that the new source of excitation generates intensive impulse activity, which overcomes the numerous synaptic delays and spreads to practically every motoneuron. The fact that excitation of motoneurons persists for a long time after the end of stimulation indicates that the hyperactive determinant structure (DDS) functions as a generator of enhanced excitation which, once it has been triggered, needs no further triggering stimulation. The periodic paroxysmal synchronized discharges (Fig. 2) are evidence of spontaneous excitation of the generator's neurons.

The data in Figs. 1 and 2 indicate that the regimes of operation of the two generators are different. The left-sided generator first produces tonic activity, which then changes into phasic. The phasic activity could arise spontaneously and could be constant. The right-sided generator produces only tonic activity. Depression of the left-sided generator by glycine led to disappearance of its characteristic pattern of activity, whereas the right-sided generator continued to function as before. The two generators are therefore independent structures, each of which generates its own characteristic pattern of activity and has its own activation channel, being excited by stimulation of the corresponding receptive fields. Stimulation from other fields or of different modalities does not activate the generator at that stage of its formation. Specificity of this kind is a characteristic feature of the determinant [9-12].

The experiments showed that if the right-sided generator was excited during activity of the left-sided generator, the effects of the latter were depressed (Fig. 2, IV). This phenomenon was not the result of depression of the motoneurons of the left-sided generator, for its reexcitation was accompanied by the appearance of its characteristic activity (Fig. 2, II). The two generators, as determinant structures, are thus not only independent formations, but they can inhibit either one another directly or the effects produced by the opposite generator.

The results indicate that the spinal and brain stem motoneurons become what is evidently a single functional pool relative to the determinant structure only when the latter produces a functional volley or, in other words, during activation of a determinant structure a dynamic system arises, the final components of which are motoneurons. The determinant behaves as a mechanism of functional organization and formation of the dynamic system.

These investigations are interesting in connection with models suitable for studying the properties and role of excitation generators in the determination of the character of epileptic activity. It will be clear from the facts described above that the same structures in the spinal cord can generate both tonic and intermittent activity. Clonic discharges arise after tonic activity only in the late stages of the process, when there is a considerable increase in the size and power of the generator, a more widespread disturbance of inhibitory mechanisms, and an increase in the excitability of the generator's neurons. This is manifested as the lowering of its triggering thresholds [5, 13-16] and as self-excitation.

The results of these investigations are also important from the standpoint of analysis of the nature of what has been called strychnine tetanus, first described by Bremer [19, 20]. We have described a similar phenomenon (strychnine-like tetanus) in ascending tetanus [1-3, 7]. This phenomenon consists essentially of the appearance of discharges of motoneurons along the whole length of the spinal cord during poisoning by strychnine or tetanus toxin. Bremer [19, 20] was inclined to explain this phenomenon by periodic electrotonic excitation of the whole column of motoneurons as a physically united formation. The results of the present experiments indicate that this phenomenon is based on the formation of an excitation generator as a hyperactive determinant structure, relative to which all the motoneurons constitute a single functional pool. Synchronized excitation of motoneurons is due to impulses from the generator to all motoneurons. Blocking the excitation generator with glycine leads to disappearance of the synchronized motoneuron activity and to the abolition of the entire phenomenon.

LITERATURE CITED

1. G. N. Kryzhanovskii, in: Current Problems in the Physiology and Pathology of the Nervous System [in Russian], Moscow (1965), pp. 131-151.
2. G. N. Kryzhanovskii, Tetanus [in Russian], Moscow (1966).
3. G. N. Kryzhanovskii, in: The Integrative Activity of the Nervous System under Normal and Pathological Conditions [in Russian], Moscow (1968), pp. 21-35.
4. G. N. Kryzhanovskii, in: General Neurophysiology and Experimental Pathology of the Nervous System (Transactions of the Institute of Normal and Pathological Physiology, Academy of Medical Sciences of the USSR, Vol. 13) [in Russian], Moscow (1970), pp. 43-46.

5. G. N. Kryzhanovskii, in: Convergence and Synapses [in Russian], Moscow (1973), pp. 109-112.
6. G. N. Kryzhanovskii, Patol. Fiziol., No. 4, 3 (1973).
7. G. N. Kryzhanovskii, in: Simulation of Diseases [in Russian], Moscow (1973), pp. 120-132.
8. G. N. Kryzhanovskii (Kryzhanovsky), Arch. Exp. Pathol. Pharmacol., 276, 247 (1973).
9. G. N. Kryzhanovskii (Kryzhanovsky), in: International Congress of Physiological Sciences. Abstracts, Vol. 11, New Delhi (1974), p. 159.
10. G. N. Kryzhanovskii, in: Abstracts of Proceedings of Symposia of the Twelfth Congress of the I. P. Pavlov All-Union Physiological Society [in Russian], Vol. 1, Leningrad (1975), pp. 165-166.
11. G. N. Kryzhanovskii, Zh. Nevropatol. Psikhiatr., No. 11, 1730 (1976).
12. G. N. Kryzhanovskii, Fiziol. Cheloveka, 2, No. 6, 891 (1976).
13. G. N. Kryzhanovskii and V. K. Lutsenko, Neirofiziologiya, No. 3, 234 (1975).
14. G. N. Kryzhanovskii (Kryzhanovsky), et al., Exp. Neurol., 50, 387 (1976).
15. G. N. Kryzhanovskii, F. D. Sheikhon, and M. B. Rekhtman, Neirofiziologiya, No. 6, 608 (1975).
16. V. K. Lutsenko and G. N. Kryzhanovskii, Neirofiziologiya, No. 5, 509 (1975).
17. Yu. S. Sverdlov, Fiziol. Zh. SSSR, No. 8, 941 (1960).
18. Yu. S. Sverdlov, Neirofiziologiya, No. 1, 25 (1969).
19. F. Bremer, Arch. Int. Physiol., 51, 211 (1941).
20. F. Bremer, in: The Spinal Cord (Ciba Foundation Symposium), London (1953), pp. 78-83.
21. V. B. Brooks, D. R. Curtis, and J. C. Eccles, J. Physiol. (London), 135, 655 (1957).
22. D. R. Curtis and W. C. De Groat, Brain Res., 10, 208 (1968).
23. D. R. Curtis and G. A. R. Johnston, Ergeb. Physiol., 69, 97 (1974).
24. R. Werman, R. A. Davidoff, and M. N. Aprison, Nature, 214, 681 (1967).
25. R. Werman, R. A. Davidoff, and M. N. Aprison, J. Neurophysiol., 31, 81 (1968).